indicative of the development of prostate cancer. Accordingly, the article does not assert that the present invention does not work. Rather, it reiterates that the invention does work.

The Examiner has specifically asserted that "in their own words the authors state (page 75, first column, 2nd full paragraph) "the results of the study were unexpected and did not support the previous evidence that inhibin-α subunit was downregulated in men's prostate cancer."

This statement does appear in the Risbridger article. However, the Examiner appears to have ignored the rest of the article. This particular statement merely articulates the starting point of the analysis and discussion which forms the basis of Risbridger. However, it does not in any way reflect the nature of the final conclusion which the authors reach. As articulated in this article, a number of biopsy samples from men who had undergone radical prostatectomy were identified that exhibited an increase in levels of inhibin. It was this finding which alerted the authors to an existence of the apparent paradox in relation to inhibin levels and which then formed the basis for a more detailed analysis in relation to inhibin expression. This analysis ultimately led to the conclusions presented in the Risbridger article. These conclusions both explaining the "paradox" and re-emphasize the fact that a downregulation in inhibin levels is indicative of the development of prostate cancer. Accordingly, it appears that the Examiner did not read the entirety of the article.

In terms of the identification of the "paradox," the particular paragraph to which the Examiner makes reference also points out that the samples which had been analyzed and which showed an increase in inhibin levels were largely samples taken from men who exhibited high grade cancer, that is, cancer which was likely to metastasise. This is ultimately a crucial point since it explains this "paradox."

As a preliminary point, in order to understand the significance of these results the Examiner must understand the nature of the onset and progression of prostate cancer. Specifically, cells which undergo malignant transformation pass through a sequence of stages. Initially there will likely occur pre-malignant changes to these cells followed by their shift into a malignant state. Within the context of the malignant state, cells which are in the earlier stages of malignancy may appear to be

more differentiated than cells which have passed through to the more advanced stages. In general, all cancer cells exhibit a less differentiated form than normal cells, this reflecting the fact that in the transition to malignancy, normal cells undergo de-differentiation. Accordingly, when examining prostate biopsies, one or more of a range of cell types may be observed depending on the particular stage of the cancer being examined. Since malignant cells can undergo progressive de-differentiation as the cancer progresses, one may observe more highly differentiated cells in early onset cancer and less differentiated cells in more advanced cancer, such as metastatic cancer (this being the most advanced form of cancer).

The experimental results which the Examiner has focused on are results obtained from high grade prostate cancers, these being cancers which are the most likely to metastasise.

In terms of the paper cited by the Examiner, once the authors pointed out the existence of these paradoxical results, they went on to discuss these results and to explain the observation of the increase in inhibin levels in these samples relative to the notion that a decrease in inhibin levels is indicative of the development of prostate cancer. To this end, the Examiner's attention is drawn to point 4 on page 74 of the article which is entitled "Resolution of the paradox." In the context of this section, the paradox is clearly explained. Specifically, the authors acknowledge that prostate cancer is a multi-step process which involves an initial transition from non-malignant to malignant status and ultimately progression of the malignant status from a localized prostate cancer to a metastatic disease. The authors clearly assert that the inhibin molecule is decreased in its level of expression in the early stages of the disease but, in the context of the transition to metastatic disease, has become overexpressed.

These findings reflect the fact that most cytokines, such as inhibin, are extremely pleiotropic and do exhibit more than one type of activity. In the context of prostate cancer, the tumor suppressing activity of inhibin is required in order to prevent the transition of prostate tissue from a non-malignant to a malignant state. Where inhibin levels become decreased, this transition occurs and prostate cancer develops. However, as prostate cancer progresses from a low grade state to a more advanced state, there can occur a switch in function and expression of the inhibin molecule

such that it becomes oncogenic and causes transition into the highest grade state and metastatic disease. The switch to an oncogenic state is associated with an increase in inhibin levels.

Accordingly, a switch in the functional activity of inhibin from being a tumor suppressor molecule in the healthy prostate and during the early stages of prostate cancer through to being a pro-oncogenic molecule which can cause a low to medium grade prostate cancer to be pushed into a highly aggressive metastatic form occurs. This is explained in the text which appears in the bottom half of the second column at page 75 of the Risbridger article.

In terms of the present invention, there is therefore absolutely **nothing** inconsistent between this theory and the method which is claimed. The present invention is directed to a screening method whereby the observation of a decrease in the level of inhibin relative to normal levels is indicative of a mammal having developed prostate cancer. This remains completely true in that any male who is identified as exhibiting lower than normal levels of inhibin is indicated as having developed prostate cancer. The increases in inhibin levels to which the Examiner refers may be observed in the context of men who have relatively advanced prostate cancer, this then being an indicator of the transition to a metastatic state. However, this particular finding is not relevant to the present invention which is merely based on the fact that in patients exhibiting decreased levels of inhibin, prostate cancer has developed. This fact remains true and consistent and is highly valuable in terms of screening the male population. The fact that this method may not identify patients with metastatic disease is irrelevant since the invention as claimed is directed to the utility of a low level of inhibin being a reliable indicator of prostate cancer development in men who exhibit this characteristic, rather than the converse notion that all forms of disease related to prostate cancer development, including metastatic disease, are characterized by a decreased level of inhibin. Accordingly, the present invention provides a valuable technique for identifying a very significant population of individuals who have developed prostate cancer.

Since the specification enables the pending claims and since the Risbridger article does not contradict this, the rejection of claims 58, 60-63, 69, 72-91, 93, 95, 96, 98, and 99 under 35 USC 112, first paragraph, should be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Attorney Docket No. **229752000800**.

Dated: July 20, 2006

Respectfully submitted,

By _____
Jonathan Bockman
Registration No.: 45,640
MORRISON & FOERSTER LLP
1650 Tysons Blvd, Suite 300
McLean, Virginia 22102
(703) 760-7769